REMARKS

Applicant thanks the Examiner for withdrawing the finality of the previous Office Action in view of Applicant's timely filing of a Request for Continued Examination and payment of the required fee. Applicant also thanks the Examiner for entering the Terminal Disclaimer filed in response to the previous Office Action, and withdrawal of the obviousness-type double patenting rejection over U.S. Patent Nos. 6,426,342; 6,610,681; and 6,627,625.

Disposition of the Pending Claims

Claims 2, 3, 5, 6 and 11 are currently undergoing examination. Claims 1, 4, 7-10, and 12-17 are withdrawn from consideration. Applicant respectfully points out that, in the Office Action of May 21, 2010, the Examiner has mistakenly excluded claim 4 from the list of withdrawn claims. Thus, throughout the Office Action, the Examiner has erroneously included claim 4 along with the claims undergoing examination. For the sake of accuracy and consistency, in the following sections Applicant has limited the discussion only to claims 2, 3, 5, 6 and 11, and properly considered claim 4 to have been withdrawn.

Rejections under U.S.C. § 112, 1st paragraph (New Grounds of Rejection)

The Examiner has rejected claims 2, 3, 5, 6 and 11 under U.S.C. § 112, 1st paragraph, for allegedly failing to comply with the written description requirement, contending that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that the specification as originally filed fails to provide adequate written description for an amount of clavulanic acid salt(s) or active ester form(s) thereof that hydrolyze *in vivo* to clavulanic acid effective either to modulate neurogenic carboxypeptidase or transpeptidase activity in the brain (claim 11) or to provide a cognition enhancing concentration of clavulanic acid in the brain (claim 2). The Examiner goes into great length to support the contention that the specification lacks any specific description of the amounts of clavulanic acid that would fall within the instantly claimed genera of amounts that would achieve the claimed effects; or that the specification provides no disclosure beyond the generic disclosure

of the required function that would correlate a particular amount to performance of the claimed function that would be readily identifiable to one of skill in the art.

Applicant respectfully traverses this rejection for alleged failure to comply with the written description requirement. Applicant disagrees with the Examiner's contention that the therapeutically effective amounts of clavulanic acid are described in the specification in functional terms only. Throughout the specification, including the examples, what constitutes effective amounts of clavulanic acid that would achieve the claimed effects is described both conceptually and numerically. For example, specific amounts and ranges of clavulanic acid are expressly stated, e.g., at page 5, lines 4-5; page 7, lines 24-25; page 24, lines 25-27; page 25, lines 6-7 and 16-18; page 30, lines 15-17; page 31, lines 25-26; page 32, lines 6-14; page 33, lines 21-22; page 35, lines 22-28; page 37, lines 14-15; page 40, lines 21-22; page 42, lines 20-21; and page 44, lines 32-34. Additionally, Figure 1 shows a range of concentrations of clavulanic acid (0.1 ng/kg-1000 ng/kg) reflecting an effective dose against anxiety of 10 ng/kg body weight. Accordingly, Applicant asserts that the Examiner is in error to allege that the effective amounts of clavulanic acid are described in the specification in functional terms only.

Applicant also strongly disagrees with the Examiner's contention that a person of ordinary skill in the art "would have to undertake extensive hit and miss testing to determine the full scope of the genera of amounts claimed, ..." (Office Action, page 4, lines 12-13). It is well-established in patent law that it is not required that the specification of an application expressly spell out the exact limitations of a claimed invention. Indeed, the Examiner acknowledges that "adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed." (Office Action, page 5, lines 12-13). In other words, the Applicant is not required to provide a description of that which is readily knowable by persons skilled in the art. In regard to the instant invention, considering that the effective amounts of clavulanic acid would vary considerably depending upon the age, body weight and condition of the patient as well as the route of administration and optional use of available drug formulations and/or conjugation technologies for enhancement of blood-brain barrier transport, Applicant is not required, nor is it warranted, to describe clinical trial(s) in the application that specify the exact metes and bounds of the effective amounts of clavulanic acid. A person of ordinary skill in the art

would be able to carry out simple clinical trials during the course of practicing the invention, titrate, and readily determine the effective amounts for treatment of a specific patient.

Accordingly, Applicant respectfully requests reconsideration of the rejection of claims 2, 3, 5, 6 and 11 for alleged failure to comply with the written description requirement, leading to its withdrawal.

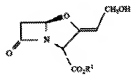
Rejections under U.S.C. § 103(a) (New Grounds of Rejection)

The Examiner has rejected claims 2, 3, 5, 6 and 11 under U.S.C. § 103(a) for alleged obviousness, contending that these claims are unpatentable over Tew *et al.* (WO 97/10247) ("Tew") in light of Cole *et al.* (U.S. Patent No. 4,110,165) ("Cole"), and in view of Yoshida *et al.* (U.S. Patent No. 4,690,949) ("Yoshida") and Pfister *et al.* (U.S. Patent No. 5,889,007) ("Pfister").

In regard to Tew, the Examiner contends that this reference teaches clavulanic acid derivative compounds of the formula shown below wherein R^1 is selected from, *inter alia*, OH, etc., and R^2 is selected from, *inter alia*, $OC_{1\text{-}6}$alkyl; that Tew teaches that the compounds function as inhibitors of Lp-PLA_2, and are therefore useful in a method for treating a disease state associated with the activity of Lp-PLA_2, and include, *inter alia*, disorders that involve lipid peroxidation in conjunction with Lp-PLA_2 enzyme activity such as, *inter alia*, Alzheimer's disease; and that Tew teaches that the compounds may be formulated into liquid formulations, tablets, capsules, parenteral compositions, suppository formulations, etc., wherein, according to the Examiner, the daily dosage regimen for an adult patient is considered to meet Applicant's effective amount(s) of instant claims 2 and 11.

In regard to Cole, the Examiner contends that this reference teaches that esters of clavulanic acid (*e.g.*, simple alkyl esters, such as the methyl ester) show an enhanced tendency to hydrolyze to clavulanic acid under mild conditions, *e.g.*, in water buffered to pH 7, including esters of the formula shown below, wherein R^1 is a hydrocarbon group of 1-9 carbon atoms that may be further optionally substituted. The Examiner further contends that the clavulanic acid esters of Cole are identical with certain of the esters of Tew, and,

therefore, would hydrolyze to clavulanic acid upon administration, particularly under the mild pH conditions of the body.



In regard to Yoshida, the Examiner contends that this reference teaches that dementia can be classified into clinical types depending upon etiology and includes Alzheimer's disease, senile dementia of Alzheimer type, or dementia due to cerebral vascular disease. In view of these teachings, according to the Examiner it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the compounds disclosed in Tew for treatment of Alzheimer's disease *per se* would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of dementia. The Examiner provides further arguments, leading to the conclusion that, according to the Examiner, whatever effect(s) the instantly claimed clavulanic acid ester has in treating dementia, that effect(s) must necessarily be present in the method disclosed in Tew.

In regard to Pfister, the Examiner contends that this reference teaches 10,11-methanodibenzosuberane derivative compounds, such as, *inter alia*, (2R)-anti-5-{3-[4-(10,11-difluoromethanodibenzosuber-5-yl)-piperazin-1-yl]-2-hydroxypropoxy}-quinoline, for use in enhancing bioavailability of a pharmaceutically active agent by administering to a mammal an effective amount of such a compound sufficient to increase permeation of the active agent through the blood-brain barrier. The Examiner further contends that Pfister teaches that this enhancement of permeation of the active agent through the blood-brain barrier is a result of the interaction of the compound with the P-glycoprotein drug efflux pump to block the pump. According to the Examiner, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use and administer the compound (*i.e.*, the 10,11-methanodibenzosuberane compound of Pfister) in combination with the clavulanic acid derivative of Tew for the treatment of Alzheimer's disease, with the knowledge that the compound would increase the permeation of the agent (*i.e.*, the clavulanic acid derivative) through the blood-brain barrier. The Examiner adds that the person of ordinary skill would have been motivated to do so in order to increase plasma concentrations of the active agent to

effective levels as well as to enhance penetration into the brain to treat damaged neuronal cells.

Applicant traverses the Examiner's rejection of claims 2, 3, 5, 6 and 11 under U.S.C. § 103(a) for alleged obviousness, strongly disagreeing with the Examiner on a number of points. In regard to Tew, the subject matter of this reference is the treatment of atherosclerosis with various clavulanic acid derivatives. Simple C_{1-6}alkyl esters of clavulanic acid are included among those various derivatives. A sweeping generalization is made in Tew to the effect that, because the compounds therein are inhibitors of Lp-PLA_2, these compounds may have a general application in any disorder that involves endothelial dysfunction (e.g., atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion). Tew goes on to make an even more sweeping generalization to the effect that the compounds therein may have a general application in any disorder that involves lipid peroxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation. No evidence whatsoever, e.g., animal testing data, is provided in Tew in support of these sweeping and unfounded generalizations.

The Examiner concedes that Tew fails to teach "that the patient suffering from Alzheimer's disease also suffers from dementia..." However, the Examiner turns to the Yoshida reference and uses it to bridge the gap and nullify Applicant's claim to the treatment of dementia (instant claim 3). In Yoshida, whose subject matter is a compound of a chemical class unrelated to clavulanic acid and that is claimed as a therapeutic drug for dementia, a statement is made to the effect that dementia could be classified into various clinical types according to etiology, such as Alzheimer's Disease, senile dementia of Alzheimer type, and dementia due to the cerebral vascular diseases. Thus, the Examiner uses Yoshida to equate Alzheimer's disease with dementia, combines the teaching of Yoshida with that of Tew, and concludes that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the disclosed compound(s) of Tew for the treatment of Alzheimer's disease *per se* would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of dementia..."

Applicant respectfully contends that the Examiner's reasoning is erroneous in several respects. Firstly, Applicant suggests that in combining the unrelated teachings of Tew and Yoshida the Examiner has engaged in hindsight construction, which is impermissible and does not accord with U.S. patent law. Thus, the Examiner resorts to cherry picking information from the published literature, and provides no credible rationale whatsoever as to why a person of ordinary skill in the art would combine the teaching of Tew with the unrelated teaching of Yoshida to arrive at the claimed invention. Applicant suggests that the Examiner has improperly used Applicant's disclosure as a roadmap to navigate Tew and Yoshida and cobble together isolated statements made in these unrelated references to arrive at a semblance of Applicant's invention. Merely combining a collection of individual statements from unrelated references without any credible rationale for why a person having ordinary skill in the art would combine these disparate statements to arrive at Applicant's claimed invention is improper, and contravenes the premise that the "invention as a whole" must be rendered obvious under Section 103, as indicated in MPEP § 2141.02 ("In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious").

Secondly, the aforementioned sweeping and unsupported generalized statements of Tew in regard to diseases that <u>may</u> be treatable with the compounds therein cannot be properly used in support of an obviousness rejection, especially that Tew juxtaposes together in the same list various diseases that have nothing to do with each other, such as Alzheimer's disease (a neurological disease), myocardial infarction (a circulatory disorder), and other primary diseases (atherosclerosis, diabetes, hypertension, angina, ischaemia, reperfusion; all of which are circulatory disorders). A person of ordinary skill in the art, upon reading Tew's sweeping, generalized statements and incredible list of unrelated diseases, with unrelated underlying modes of action, would completely disregard and ignore Tew's teaching.

Thirdly, the Examiner's reliance on Yoshida to equate Alzheimer's disease with dementia is improper. Even though there might be a subset of Alzheimer's patients that also suffers from dementia, and vice versa, that patient overlap is not sufficient to equate Alzheimer's disease with dementia, or to equate a treatment for dementia with a treatment for Alzheimer's disease. For example, even a cursory search in the Internet encyclopedia

Wikipedia quickly reveals that dementias are of vastly varying types and etiologies, and the overlap of dementia and Alzheimer's disease is only minuscule at best. The Examiner states "Tew et al. provides the clear teaching that the instantly claimed clavulanic acid ester(s) is, in fact, effective for treating all Alzheimer's patients, i.e., 100% patients with Alzheimer's disease, without exclusion." (Office Action, page 8, lines 6-8). This statement is false for the reasons discussed above; Tew's sweeping generalizations, wherein diseases that are totally unrelated to each other are juxtaposed together, cannot be construed as "clear teaching" that clavulanic acid is effective for treating 100% of Alzheimer's patients.

Fourthly, and most importantly, contrary to the Examiner's assertion in regard to the teaching of Tew, Applicant points out to the Examiner the fact that Alzheimer's disease is not known to be an Lp-PLA_2 mediated disease, but is widely known to be caused by beta-amyloid dysregulation. Both of these facts can be readily confirmed by a quick search on Alzheimer's Disease in the Internet encyclopedia Wikipedia. Tew erroneously characterizes clavulanic acid and esters as being exclusively inhibitors of Lp-PLA_2. As additional support of the fact that Alzheimer's disease is not known to be an Lp-PLA_2 mediated disease, Applicant makes reference to the following publications, a copy of each of which is transmitted herewith in the accompanying Information Disclosure Statement:

Schaloske, R.H.; Dennis, E.A., "The phospholipase A_2 superfamily and its group numbering system," *Biochimica et Biophysica Acta*, 1761(11):1246-1259 (2006). This review article discusses the PLA_2 superfamily of enzymes. On page 1250 therein it is stated, "One of these enzymes is secreted, namely the GVIIA PLA_2. This enzyme is also known as plasma PAF-AH or lipoprotein-associated PLA_2 (Lp-PLA_2)." Also on page 1250 it is stated, "This activity has been the subject of interest since it may have potentially beneficial effects by inhibiting the progression of atherogenesis (reviewed in [131,132]). However, this issue is controversial (reviewed in [133,134]) and it has been suggested that GVIIA PLA_2 is rather a positive risk factor for coronary disease and that quantification of GVIIA PLA_2 levels in the plasma might help to predict the risk for individuals to develop cardiovascular disease." There is no mention of Alzheimer's disease anywhere in this article.

Farooqui, A.A.; Ong, W.-Y.; Horrocks, L.A., "Inhibitors of Brain Phospholipase A_2 Activity: Their Neuropharmacological Effects and Therapeutic Importance for the Treatment of Neurologic Disorders," *Pharmacol. Rev.*, 58:591-620 (2006). Lp-PLA_2 is not mentioned in this review article. However, even in regard to other PLA_2 enzymes, it is

stated on page 609 therein, "At this stage it is not known whether elevation of $cPLA_2$ and PlsEtn-PLA_2 activities is the cause or the consequence of neurodegenerative process and whether changes in activities of PLA_2 isoforms are primary or secondary. Thus, more studies on the involvement of PLA_2 isoforms in pathogenesis of AD are required."

Bhatti, S.; Hakeem, A.; Cilingiroglu, M., "Lp-PLA_2 as a Marker of Cardiovascular Diseases," *Curr. Atherscler. Rep.*, 12:140-144 (2010). In this review article, the relationship between Lp-PLA_2 and cardiovascular disease is discussed. However, there is no mention whatsoever of Alzheimer's disease.

Karakas, M.; Koenig, W., "Lp-PLA_2 Inhibition – The Atherosclerosis Panacea?" *Pharmaceuticals*, 3:1360-1373 (2010). In this reference, the relationship between Lp-PLA_2 and cardiovascular disease is discussed. However, there is no mention whatsoever of Alzheimer's disease.

Sanchez-Mejia, R.O.; Mucke, L., "Phospholipase A_2 and Arachidonic Acid in Alzheimer's Disease," *Biochimica et Biophysica Acta*, 1801(8):784-790 (2010). This review article discusses the relationship between PLA_2 and Alzheimer's disease. However, there is no mention anywhere in this article of Lp-PLA_2 and Alzheimer's disease.

Applicant is unaware of any publication wherein Alzheimer's disease is considered to be mediated by Lp-PLA_2. Likewise, the cited references above, and others like them, make it clear that persons of ordinary skill in the art would have no reason or basis to consider Alzheimer's disease to be mediated by Lp-PLA_2.

In regard to the Cole reference cited by the Examiner, Applicant asserts that this reference is irrelevant to the instant claims. The Examiner uses this reference as proof that simple alkyl esters of clavulanic acid would slowly hydrolize to clavulanic acid under the mild pH conditions of the body. Accordingly, the Examiner relies on Cole to nullify the recitation in the instant claims of an "active ester form" that hydrolyzes *in vivo* to clavulanic acid. Applicant asserts that the slow ester hydrolysis described in Cole does not qualify Cole's esters as "active ester forms," as is well-recognized in the art and as is defined in the instant application on page 22, line 29 to page 23, line 9. It is well-known by those of ordinary skill in the art of organic chemistry what the term "active ester form" means, and that it is improper to encompass simple alkyl esters under that term. Furthermore, the half-

life of clavulanic acid in the body is reported to be 1 hour. Slow hydrolysis of a simple alkyl ester of clavulanic acid does not allow for sufficient build-up in the brain of an effective amount of clavulanic acid that renders the claimed therapeutic effect.

In regard to the Pfister reference cited by the Examiner, Applicant likewise contends that this reference is irrelevant in regard to the instant claims. Applicant acknowledges that Pfister teaches the use of the same P-glycoprotein efflux pump inhibitor disclosed in the instant application for enhancing bioavailability of the active agent. However, the P-glycoprotein efflux pump inhibitor recited in instant claims 5 and 6 does not stand alone; this agent is recited as being co-administered with the active agent (clavulanic acid, salt or active ester form) in a method for providing a cognition enhancing concentration of clavulanic acid in the brain of the patient (claims 11 and 2). In view of Applicant's foregoing arguments, particularly in regard to the teachings of Tew and Yoshida, Applicant submits that the teaching of Pfister is rendered moot.

Accordingly, Applicant respectfully requests reconsideration of the rejection of claims 2, 3, 5, 6 and 11 for alleged obviousness over Tew in light of Cole, and in view of Yoshida and Pfister, leading to its withdrawal.

CONCLUSION

Applicant believes that the foregoing remarks are fully responsive to the Examiner's Official Action mailed May 21, 2010, and that the claims of the instant application are now in condition for allowance leading to issuance. Such action is respectfully requested.

Respectfully submitted,
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